The opinion in support of the decision being entered today is *not* binding precedent of the Board.

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Ex parte SOLOMON S. STEINER and BRYAN R. WILSON

Appeal 2007-0318
Application 09/766,362
Technology Center 1600

Decided: July 25, 2007

Before ERIC GRIMES, LORA M. GREEN and NANCY J. LINCK, *Administrative Patent Judges*.

LINCK, *Administrative Patent Judge*.

DECISION ON APPEAL

This is a 35 U.S.C. § 134 appeal in the above-referenced case.[1]

We have jurisdiction under 35 U.S.C. § 6(b). We affirm.

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[1] The application was filed January 19, 2001. The real party in interest is MannKind Corporation.

STATEMENT OF THE CASE

The Specification

The field of the invention is "pharmaceutical formulations, and more particularly related to methods and compositions for nasally administering antihistamines." (Specification (hereafter "Spec.") 1.)

According to the Specification: "Azelastine hydrochloride is a potent, long acting antihistamine currently administered via the intranasal route in an aqueous solution . . . ." (Spec. 1.) When used in this form, it "imparts a long lasting, very bitter taste." (*Id.*)

The Specification summarizes the invention as follows:

> Dry powder formulations of drugs such as anti-histamine for nasal administration are provided where the drug is retained in the nasal cavity, and systemic side effects minimized or eliminated, *through the selection of a narrow particle size range, between approximately 10 and 20 microns* in diameter. In a preferred embodiment wherein the drug is an antihistamine, retention of the antihistamine at the nasal mucosa is improved and the bitter aftertaste associated with liquid antihistamine formulations significantly reduced. By making a dry powder formulation of an antihistamine (e.g., azelastine) having an average particle size of between 10 and 20 microns, the antihistamine is restricted primarily to the desired target organ, the nasal mucosa. Because the active ingredient stays in the nasal region, a lower dose can be used to achieve the same desired effect. As demonstrated by the examples, . . . this formulation does not impart a bitter taste.

(Spec. 2 (emphasis added).)

There are five examples in the Specification. Examples 1 and 2 each disclose a dry powder formulation having "an average particle size of between 10 and 20 microns" but also having a relatively wide "particle size

range," i.e., greater than 3.15 to 32.20 and 2.99 to 43.52 microns, respectively. (Spec. 13-14 (disclosing the particle size ranges for 10 to 90% of the particles).)

Example 3 compares administration of the dry formulations of Examples 1 and 2 (according to the claimed invention as filed) with the same formulations in liquid form. (Spec. 14.) The comments of the three volunteers suggested the dry formulations at least "markedly reduce[ed] the bitter taste and after taste associated with the . . . liquid nasal spray of azelastine." (Spec. 15.)

Example 4 exemplifies dry powder formulations of chlorpheniramine "made and tested with similar good results" as Examples 1 and 2. (*Id.*)

Example 5 (the only example within the scope of the pending claims) discloses antihistamine formulated in diketopiperazine:

> Diketopiperazine particles (10 to 20 microns in diameter) were suspended in aqueous medium. Antihistamine was added, the suspension acidified, and the suspension lyophilized to yield antihistamine powder.
>
> Results of administration to volunteers were similar to the results obtained in examples 1-4.

(*Id.*)

The Claims on Appeal

The following claims are representative of each group argued:[2]

1. A composition for the nasal administration of a drug in a dry powder form suitable for administration to the nasal region,

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[2] The following groups of claims are argued: claims 1, 2, 4, and 5; claims 7, 9, 11, and 12; claims 14, 15, 17, and 18; claims 3, 8, 10, and 16; and claims 20 and 21. With respect to each of these groups, we consider the representative claim (quoted above), pursuant to 37 C.F.R. § 41.37(c)(1)(vii) (2006).

the dry powder form comprising microparticles having an average particle size of between 10 and 20 microns and comprising the drug and diketopiperazines.

7. A drug delivery device for nasal administration comprising a drug in a dry powder form . . . , and a device for delivering a measured dose of the drug to the nasal mucosa, wherein the dry powder form comprises [the composition of claim 1].

14. A method for administering a drug to the nasal region of a patient in need thereof, comprising nasally administering a dry powder . . . , wherein the dry powder comprises [the composition of claim 1.]

3. The composition of claim 2 [wherein the drug is selected from the group consisting of antihistamine, vasoconstrictors, antiinflammatories and analgesics] wherein the antihistamine is selected from the group consisting of chlorpheniramine and azelastine.

20. The composition of claim 1 formed by spray drying.

The Examiner relies upon the following references to support his two 35 U.S.C. § 103(a) rejections:

Steiner	U.S. 5,503,852	Apr. 2, 1996
Illum	U.S. 5,690,954	Nov. 25, 1997

Claims 1, 2, 4, 5, 7, 9, 11, 12, 14, 15, 17 and 18 are rejected over Steiner; and claims 3, 8, 10, 16, 20, and 21 are rejected over Steiner and Illum.

OBVIOUSNESS UNDER § 103(a)

THE REJECTIONS BASED ON STEINER

Claims 1 and 14

Claim 1 recites a composition, and claim 14 recites the administration of the compound. With respect to claim 1, Appellants contend:

> Steiner does not disclose drug delivery systems suitable for nasal administration nor suggest a composition of microparticles having an average size between 10 and 20 microns. Steiner does not disclose or suggest modifying the particles for administration in a dry powder form to the nasal mucosa. Thus Steiner does not provide the necessary motivation to one of ordinary skill in the art to modify its particles so that they are suitable for nasal administration. Therefore independent claim 1 and dependent claims 2, 4 and 5 are non-obvious over Steiner.

(Second Substitute Appeal Brief (rec'd Dec. 27, 2005) (hereafter "App. Br.") 10.)

Appellants' arguments regarding the patentability of claim 14 track those made with respect to claim 1:

> Independent claim 14 and its dependent claims define a method for administering a drug to the nasal region of a patient. Claim 14 specifies that the method requires nasally administering a dry powder suitable for nasal administration. Steiner does not disclose or suggest nasally administering a dry powder. . . . [T]he only reference to the nasal tract occurs when Steiner mentions that microparticles can include a diagnostic imaging agent useful for imaging the nasal tract. However, Steiner does not disclose the form in which the microparticles are administered to image the nasal tract. Further, Steiner does not suggest nasal administration of a dry powder.

(App. Br. 11-12.)

The Examiner responds:

> Steiner *et al.* teach drug delivery systems based on the formation of diketopiperazine microparticles and microencapsulation of drugs by derivatives of diketopiperazine, wherein the microparticles are formed in the presence of the drug to be delivered and the microparticles are between 0.1 to 10 microns in diameter and whereby the microparticles are used for diagnostic

> applications, especially for imaging of the nasal tract (see reference col. 4, lines 30-55); (col. 10, lines 25-49); (col. 13, lines 13-24) and abstract. . . . Appellant's argument that 'Steiner does not disclose dry powder formulations' is not persuasive since the formulation of Steiner is a microparticulate *(i.e.,* powder) formulation.

(Answer 7-8.)

With respect to the particle size limitation, the Examiner continues:

> It is noted that the particles of Steiner having a particle size of 10 microns would be retained in the mucosal cavity for sufficient drug delivery. . . . A review of the instant specification indicates that formulations I and II on pages 13 and 14, respectively, have particles with micron sizes that are less than 10 microns. Specifically, Formulation I on page 13 demonstrates that *10%* of particles had a particle size of only *3.15* microns. Similarly, Formulation II on page 14 demonstrates that *10%* of particles had a particle size of only *2.99* microns. . . . Therefore, this clearly establishes that the 'between 10 microns' claimed by Appellants is not a critical lower . . . particle size limitation.

(Answer 8-9 (emphasis in original).)

With respect to claims 1 and 14, we frame the § 103(a) issues:

Would the dry powder formulation of claim 1 "comprising microparticles having an average particle size of between 10 and 20 microns and comprising the drug and diketopiperazines" have been obvious to the skilled artisan in view of Steiner's disclosure of microparticles having a particle size range between 0.1 and 10 microns and comprising a drug and diketopiperazines? (Claim 1.)

Would it have been obvious to the skilled artisan to nasally administer the dry powder formulation of claim 1? (Claim 14.)

FINDINGS OF FACT RELATING TO CLAIMS 1 AND 14[3]

Claim Interpretation

1. Claim 1 is to a composition which includes microparticles of a drug and deketopiperazine wherein the microparticles have "an average particle size of between 10 and 20 microns."

2. The claim language "having an *average* particle size of between 10 and 20 microns" does not restrict the particle size *range* to a specific or narrow range and includes the ranges disclosed in Examples 1 and 2 of the Specification. (Spec. 13-14.)

3. "Drug" is not defined in the Specification. Its broadest reasonable interpretation includes "a substance intended for use in the diagnosis . . . of disease" (Webster's New Collegiate Dictionary (1977) (hereafter "Webster's") 350), and thus includes imaging agents.

The Prior Art

4. Steiner discloses a drug delivery system comprising microparticles having a particle range from 0.1 to 10 microns and comprising a drug and diketopiperazine. (Answer 3-4 (citing Steiner, col. 4, ll. 30-55 & col. 10, ll. 25-49).)

5. Steiner's size range overlaps with and theoretically could be identical to that of the claims. For example, particles of 10 microns satisfy the claim limitation and also fall within a range between 0.1 and 10 microns. (*See* Answer 9.)

6. Steiner discloses administering "biologically active agents" including imaging agents, in combination with microparticles of diketopiperazines without any requirement the agent and/or microparticles

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[3] Findings of Fact are abbreviated "FF."

be in, e.g., a liquid or suspension. (*See, e.g.,* Steiner, col. 26, ll. 10-19 (claim 17).)

7. One skilled in the art would understand the term "microparticles" to mean very small particles, i.e., a powder. (Answer 8; Webster's 749, 858.)

8. Steiner confirms the microparticles are in a dry form by disclosing that their "microparticles can be stored in the dried state . . . ." (Steiner, col. 10, l. 9.)

9. Steiner discloses nasal administration of a drug (an imaging agent) and suggests administration in the form of microparticles, preferably microparticles "that bind to mucosal membranes." (Col. 13, ll. 13-21, *cited in* Answer 3-4.)

10. Absent evidence to the contrary, Steiner's microparticles would be "suitable for nasal administration." (FFs 4-9.)

The Differences Between Claims 1 and 14 and the Prior Art

11. With respect to both claims 1 and 14, the single, arguable difference between the claimed invention and Steiner's teachings is the claim recites an "average particle size of between 10 and 20 microns," and Steiner discloses a "particle size range between 0.1 and 10 microns." (FFs 1-3, 4-9.)

12. Based on Steiner's teachings and suggestions, one of ordinary skill in the art would have been motivated to nasally administer Steiner's microspheres comprising a drug and diketopiperazine and, if necessary, to optimize the particle size range for the particular application. (FFs 4-10.)

13. Further, the skilled artisan, knowledgeable about the administration of drugs to the nasal cavity, would have a reasonable

likelihood of successfully nasally administering Steiner's microparticles and optimizing the method, including the particle size. (FFs 4-12.)

"Unexpected Results"

14. The Specification states "systemic side effects [are] minimized or eliminated through the selection of a *narrow particle size range*, between approximately 10 and 20 microns in diameter." (Spec. 2 (emphasis added).)

15. The Specification also describes advantages of having an *average* particle size between 10 and 20 microns but refers to drug alone as well as drug and diketopiperazine microparticles. (Spec. 2.)

16. Examples 1 and 2 are to the originally claimed invention "comprising a drug in dry powder form having an average particle size of between 10 and 20 microns . . . ." (Spec. 17 (claim 1); *see also* Spec. 13-14 (Exs. 1 & 2).) Original claim 1 did not recite "microparticles" or "diketopiperazine." (Spec. 17 (claim 1).)

17. Example 3 compared the dry powder drug formulation of Examples 1 and 2 with a liquid formulation of each and concluded the liquid form resulted in a "bitter taste and after taste" in all cases, while the dry form did not. (Spec. 14-15.)

18. Example 5 is the only example encompassed by present claim 1, but even Example 5 does not reflect the full scope of the claim in that the particles of Example 5 are "10 to 20 microns in diameter" rather than of "average particle size of between 10 and 20 microns." (Spec. 15 & claim 1.)

19. The results of Example 5 "were similar to the results obtained in examples 1-4." (Spec. 15.)

20. Appellants' examples do not support their argument that an "average particle size of between 10 and 20 microns" provides "unexpected

results" compared to Steiner's disclosed range but rather provides some evidence that using a drug in dry powder form rather than in liquid form avoids a bitter taste and after taste. (FFs 14-19.)

21. There is no other teaching in the Specification to support a finding that the presently claimed invention provides unexpected results compared to the prior art formulations of Steiner.

22. Appellants have not provided any evidence of unexpected results, such as through a declaration or reference to other prior art teachings.

DISCUSSION OF STEINER REJECTION

Claims 1 and 14

The patentability of claims 1 and 14 turns on the particle size limitation. The other claim limitations are either taught or would have been clearly suggested by the teachings of Steiner, in view of what would have been generally known in the art at the time the invention was made. (See FFs 1-10.)

Claiming an "average particle size" rather than a particle size range complicates a comparison between the claimed invention and Steiner. (FFs 2, 5, 11, 14-18.) Giving Appellants the benefit of the doubt, however, there is at least an overlap between Steiner's 10 microns and the claimed 10 microns. (See FFs 4, 5.)

Overlapping ranges support a prima facie case of obviousness. *E.g., In re Peterson,* 315 F.3d 1325, 1329, 65 USPQ2d 1379, 1382 (Fed. Cir. 2003); *In re Geisler*, 116 F.3d 1465, 1469, 43 USPQ2d 1362, 1365 (Fed. Cir. 1997); *In re Woodruff*, 919 F.2d 1575, 1578, 16 USPQ2d 1934, 1936-37 (Fed. Cir. 1990). Further, the "normal desire of scientists or artisans to

improve upon what is already generally known provides the motivation to determine where in a disclosed set of percentage ranges is the optimum combination of percentages." *Peterson*, 315 F.3d at 1330, 65 USPQ2d at 1382. "The law is replete with cases in which the difference between the claimed invention and the prior art is some range or other variable within the claims. . . . These cases have consistently held that in such a situation, the applicant must show that the particular range is *critical*, generally by showing that the claimed range achieves unexpected results relative to the prior art range." *Woodruff*, 919 F.2d at 1578, 16 USPQ2d at 1936 (emphasis in original). In this case, Appellants have not shown their claimed range is "critical," i.e., produces unexpected results. (FFs 14-22.)

Based on our findings and those of the Examiner, we conclude the subject matter of claims 1 and 14 would have been obvious to the skilled artisan in view of Steiner's teachings and the skill in the art.

Claim 7

With respect to claim 7, Appellants additionally contend "Steiner does not disclose or suggest a device for delivering a measured dose of a drug to the nasal mucosa." (App. Br. 11.) The Examiner found otherwise. (*See* Answer 3-4 & 10 (discussing Steiner's application to the nasal mucosa)). Given these conflicting views, we define the claim 7 issue: Would the use of a "drug delivery device for delivering a measured dose of the drug to the nasal mucosa" have been obvious to the skilled artisan, based on Steiner's teachings regarding administering microparticles that bind to mucosal membranes for imaging of the nasal tract?

ADDITIONAL FINDINGS OF FACT RELATING TO CLAIM 7

23. Steiner discloses or suggests all the limitations of claim 7, including nasal administration of an imaging agent (FFs 4-9), but does not expressly disclose any device for nasal administration.

24. Nasal administration of drugs, including dry powder forms and appropriate devices for doing so, was known in the art. (*See, e.g.*, Illum, col. 1, l. 22 to col. 4, l. 2 (describing the prior art).)

25. Appellants' single, general disclosure in the Specification of methods of nasal administration supports the finding that such methods were well known in the art. (*See* Spec. 13, Example 1 ("The dry powder formulation can be administered by the use of a nasal insufflator . . . preferably . . . provided with means to ensure administration of a substantially fixed amount of the composition.").)

26. One skilled in the art would have known the necessity of "delivering a measured dose" of a drug nasally and would have known how to do so. (FFs 24-25.)

27. Thus, given Steiner's express disclosure of administering an imaging agent to the nasal mucosa, the skilled artisan would have known to use an appropriate "delivery device for delivering a measured dose of the drug to the nasal mucosa." (FFs 23-26.)

Discussion of the Patentability of Claim 7

Based on our findings and those of the Examiner, we conclude the subject matter of claim 7, including the delivery device, would have been obvious to the skilled artisan in view of Steiner's teachings and the skill in the art, absent evidence establishing the criticality of the claimed average particle size range. (FFs 4-9, 24-27.)

THE REJECTIONS BASED ON STEINER AND ILLUM

Claim 3

With respect to claim 3, Appellants additionally argue: "Steiner does not disclose antihistamines." (App. Br. 12.) Further, with respect to all the rejections based on the combination of Steiner and Illum, Appellants argue:

> [Illum's] bioadhesive microspheres adhere to the nasal mucosa upon contact forming a gel (col 3, lines 2-9) and have improved bioavailability due to the presence of absorption enhancers which increase the bioavailability of the drug (col. 4, line 6-12.). . . . Illum does not disclose or suggest the inclusion of diketopiperazines in the delivery system. Illum discloses microparticles with a size range between 10 and 100 microns (col. 6, lines 13-15). Illum does not suggest the selection of particles having a narrow size range of between 10 and 20 microns.

(App. Br. 12.)

Finally, Appellants argue there's no motivation to combine the two references. (App. Br. 14.)

The Examiner responds:

> Admittedly, Steiner *et al.* do not disclose antihistamines, however, Ilum was relied upon for the teachings that it is well known in the art to incorporate particles formed of antihistamines as the preferred active substance for nasally administered formulations. . . . Appellant's argument that "Illum does not disclose or suggest the inclusion of diketopiperazines" is not persuasive since Illum was not relied upon for the teaching of diketopiperazines . . . . The argument that 'Illum does not suggest the selection of particles having a narrow size range of between 10 and 20 microns' was not persuasive since the particles of Illum are taught to be in the size range of between 10 and 100 microns. This size range clearly encompasses the 'between 10 and 20 microns' claimed by Applicant.
>
> . . . .

> Appellant's argument that 'the delivery systems of Illum contain absorption enhancers to increase bioavailability and requires the formation of a gel' is not persuasive since the instant 'comprising' claim language permits the presence of additional components or additional steps aside from those recited. . . .
>
> . . . The prior art teaches the use of the same ingredients *(i.e.,* diketopiperazines, antihistamines), used for the same field of endeavor *(i.e.,*mucosal applications) to treat the same problems *(i.e.,* retention of drug in nasal cavity) as that desired by Applicants. Since the prior art recognizes and explicitly teaches drug delivery systems based on the formation of diketopiperazine microparticles and teaches the microparticles to be in a suitable size range (between 0.1 and 10 microns -Steiner & between 10 and 100 microns -Illum), the instant invention when taken as a whole, is rendered *prima facie* obvious to one of ordinary skill in the art.

(Answer 10-14 (emphasis in original).)

We frame the § 103 issue with respect to claim 3 as follows: Would it have been obvious to one of ordinary skill in the art to incorporate a vasoconstrictor, antiinflammatory, analgesic, or chlorpheniramine as the drug of claim 1 in view of Steiner's and Illum's teachings?

ADDITIONAL FINDINGS RELATING TO THE COMBINATION OF REFERENCES

28. Illum discloses a drug delivery system for nasal administration, including microsphere particles containing an active drug, including chlorpheniramine (col. 9, ll. 48-55), and having a "size between 10 and 100 microns." (Illum, col. 6, ll. 13-15.) "Preferably, the particles are administered in the form of a powder by spraying and have bioadhesive properties." (Col. 4, ll. 13-14.)

29. The claim language "comprising" does not exclude other components, such as an absorption enhancers and gel-forming materials disclosed by Illum.

30. In addition, Illum discloses administering their drugs "in powder form using a nasal insufflator," and "in the form of a powder by spraying" (col. 3, ll. 12-14; col. 4, ll. 13-14); Illum also identifies sources for nasal insufflators "employed for commercial powder systems intended for nasal application." (Col. 9, ll. 53-61.)

31. Illum explains the advantages of nasal delivery, known in the art. (Col. 1, l. 62 to col. 2, l. 3.)

32. The skilled artisan would have been motivated to combine the teachings of Steiner and Illum with a reasonable expectation of success, as both references are directed to drug delivery systems useful for administration to the nasal mucosa. (FFs 9, 28-31.) Steiner teaches the advantages of diketopiperazine (col. 4, ll. 49-55) and Illum expressly discloses the advantages of nasal administration with a dry powder form of drug via a nasal insufflator. (FF 31.)

33. Both Steiner and Illum teach relatively small particle sizes which either overlap with the claimed range (Steiner) or encompass the claimed range (Illum). (FFs 4-5, 28.)

DISCUSSION OF REJECTION BASED ON STEINER AND ILLUM

Based on our findings and those of the Examiner, we conclude claim 3 would have been obvious in view of the combination of Steiner and Illum. For the reasons given in addressing the rejection over Steiner alone, we again conclude all of the claim limitations which flow from dependency on

claim 1 would have been obvious to the skilled artisan, absent a showing of criticality, or unexpected results, due to the claimed average particle size range. (*See supra* pp. 10-11 ("DISCUSSION OF STEINER REJECTION").)

Additionally we conclude incorporating the drugs recited in claim 3 would have been obvious in view of the teachings of Steiner and Illum and also Appellants' own admissions in their Specification. (FFs 28 & 32.)

While not necessary to sustain all the rejections, the particle size range disclosed in Illum, between 10 and 100 microns, encompasses (or at least overlaps) Appellants' claimed range. Thus, Illum provides additional evidence Appellants' claimed range would have been obvious to the skilled artisan, absent evidence rebutting the prima facie case of obviousness created by the range overlap. (*See* FFs 14-22, 28, & 33 and the discussion *supra* pp. 10-11.)

Claim 20

With respect to claim 20, Appellants argue "neither Steiner nor Illum disclose forming the microparticles by spray drying . . . ." (App. Br. 16.) We find "[s]pray drying methods . . . are well known in the art," as Appellants admit. (Spec. 3.) Thus, we further conclude claim 20 would have been obvious to one of ordinary skill in the art based on Steiner and Illum, in view of Appellants' admission regarding spray drying methods.

CONCLUSION

In summary, we affirm the Examiner's § 103(a) rejections of claims 1, 7, 14, 3, and 20 over the cited prior art. Pursuant to 37 C.F.R.

§ 41.37(c)(1)(vii)(2006), we also affirm the § 103(a) rejections of claims 2, 4-6, 8-12, and 15-20, as these claims were not argued separately.

No time period for taking any subsequent action in connection with this appeal may be extended under 37 C.F.R. § 1.136(a)(1)(iv)(2006).

AFFIRMED

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